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TECHNICAL NOTE

XAD-4 resin hemoperfusion for digitoxic patients with renal failure

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In normal subjects the major route of digoxin elimination is renal, with digoxin clearance approximating glomerular filtration rate; the maintenance of good renal perfusion and urine flow is vital for the resolution of digoxin toxicity. In subjects with renal failure digoxin half-life is much prolonged [1] and digoxin toxicity can be protracted. We report the clinical course and characteristics of XAD-4 hemoperfusion in three patients with renal failure and refractory manifestations of digoxin toxicity.

Methods and Results. Conduct of hemoperfusions. Cartridges of XAD-4 resin were used for each hemoperfusion (HP). Inflow (A) and outflow (V) blood samples were taken regularly for digoxin measurements. Plasma digoxin was quantified by radioimmunoassay. RBC-surface digoxin and total RBC digoxin were measured by radioimmunoassay with Immunobeads and I^{125} digoxin tracer (Quantimmune Digoxin RIA Kit, Bio-Rad Laboratories, Richmond, California) with preparations of washed packed unlysed and lysed RBCs. The extraction fraction of digoxin by the resin was calculated (A–V/A) and the digoxin clearance from plasma and RBCs cells derived. Digoxin was eluted from the used columns by methanol extraction and quantitated [2]. Mean digoxin clearance was calculated from the amount of digoxin recovered (digoxin recovered/mean inflow digoxin concentration).

Case reports: Patient 1 (Table 1). The patient had chronic renal failure and had been taking 0.125 mg digoxin per day. She developed nausea, vomiting, abdominal pain, diarrhea, blurred vision, distorted color perception, variable first and second degree and complete heart block (ventricular rate of 28/min), and multiple ventricular premature beats (VPBs). There was no improvement over 48 hr, so XAD-4 HP was undertaken. During HP rhythm changed to sinus mechanism with first degree heart block at 60 to 70 beats/min, and VPBs subsided. Noncardiac symptoms resolved and did not recur. Several hours after HP second degree heart block with VPBs recurred, so HP was repeated. During treatment the arrhythmias resolved permanently. The P-R interval and heart rate normalized.

The extraction of digoxin from the plasma remained excellent throughout both procedures. Calculated mean plasma digoxin clearances were 156 ml/min for the first treatment and 167 ml/min for the second treatment. The plasma T½ of digoxin shortened dramatically during each HP. The amount of digoxin recovered from the cartridge exceeded the calculated quantity of digoxin extracted from the plasma, suggesting that digoxin was also being cleared from formed blood elements, perhaps RBCs [2]. The whole blood digoxin clearance, calculated from recovered digoxin, was 218 ml/min for the first HP and 293 ml/min for the second HP. Plasma digoxin rebounded to a level intermediate between pre- and postperfusion values after each hemoperfusion. The 342 μg removed during 11 hr of HP represents 65.8% of an ideal intravenous loading dose (10 μg/kg), or four pills of 0.125 mg at 67% absorption [1], or 4 days' worth of her previous maintenance dose.

Patient 2 (Table 2). This diabetic maintenance hemodialysis patient, became digitoxic, with intractable nausea and vomiting and profound hypotension during dialysis. Digoxin was discontinued, but symptoms worsened over the next 48 hr. HP was undertaken using a forearm fistula for blood access. Nausea and vomiting cleared dramatically. Treatment was discontinued when the arterial needle became dislodged. Hemodialysis was then conducted without complications. The digoxin level rebounded to 5.2 ng/ml but his symptoms remained improved; hemodialysis was again uneventful and HP was not repeated.

Extraction of digoxin from the plasma was excellent and well maintained. Plasma T½ of digoxin was reduced dramatically. RBC-surface digoxin concentration was approximately equal to that of plasma, and digoxin was extracted with efficiency approaching that of plasma digoxin extraction. Calculated digoxin removal in a 5.25-hr treatment was 246 μg, or 3 days' worth of his previous maintenance dose at 67% absorption, or 34% of a therapeutic loading dose.

Patient 3 (Table 3). A patient with atrial fibrillation and congestive heart failure underwent surgery for small bowel

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Table 1. XAD-4 hemoperfusion in patient 1: 40 years old, female, 52 kg, Ht 25%, K^+ 4.7 mEq/liter, C_{Cr} 3 ml/min

Time *hours*	Q_B	Q_P	Plasma digoxin A	V	EF	Cl	T½	Dig R *μg*	Cl_B (Dig R)
Pre HP #1									
−44.5			6.9						
−6.5			4.8						
HP #1							68		
Start									
0			4.3						
0.5	190	141	3.6	<0.5[a]	0.95	131			
1.5	212	157	2.9	0.5	0.83	130			
2.5	212	157	2.4	0.5	0.79	124	5.8	163	218
3.5	250	190	2.3	<0.5	0.89	169			
4.5	250	190	2.3	0.6	0.74	141			
5.5	250	190	2.2	0.5	0.77	146			
End									
7.5			3.0						
9.5			3.2						
13.5			3.3				72		
17.5			3.3						
25.5			3.0						
HP #2									
Start									
0			3.0	<0.5					
1	250	195	2.0	<0.5	0.88	171			
2	250	195	1.8	<0.5	0.86	168			
3	250	195	1.6	<0.5	0.83	161	5.6	179	293
4	250	195	1.4	<0.5	0.82	160			
5	250	195	1.3	<0.5	0.81	157			
6	250	195	1.3	<0.5	0.81	157			
End									
14			2.6						
38			2.6						

Abbreviations: Ht, hematocrit; K^+, serum potassium concentration; C_{Cr}, creatinine clearance; HP, XAD-4 hemoperfusion; Q_B, blood flow rate in milliliters per minute; Q_P, calculated plasma flow rate in milliliters per minute; A, inflow digoxin concentration in nanograms per milliliter; V, outflow digoxin concentration in nanograms per milliliter; Plasma T½ digoxin, disappearance half-time of digoxin from plasma; EF, digoxin extraction fraction; Cl, digoxin clearance in milliliters per minute; Dig R, digoxin recovered from used cartridge; Cl_B (Dig R), mean whole blood digoxin clearance calculated from recovered digoxin in milliliters per minute (see text).

[a] For digoxin levels <0.5 ng/ml extraction and clearance calculations are based on an assumed level of 0.25 ng/ml.

strangulation and developed acute renal failure. He received his usual maintenance dose of 0.125 mg of digoxin for 4 days and developed episodic nodal rhythm, frequent VPBs, ventricular bigeminy, and runs of ventricular tachycardia not suppressed by lidocaine. HP was performed with bifemoral venous catheterization. The episodes of nodal rhythm disappeared and the VPBs and runs of ventricular tachycardia became much less frequent and were more easily suppressed. Due to misinterpretation of the significance of high pressures in the inflow line, a fresh cartridge was substituted after 3.25 hr.

Extraction of plasma digoxin was excellent throughout the entire procedure. The plasma T½ of digoxin was shortened during HP. RBC digoxin (not shown) and RBC-surface digoxin were approximately equal, suggesting that most RBC digoxin was surface-associated. Most RBC digoxin was extracted during each pass through the cartridge, although the extraction fraction was somewhat less than simultaneous plasma digoxin extraction. The calculated total digoxin clearance at a blood flow rate of 350 ml/min was 280 ml/min, more than three times renal digoxin clearance for a comparable normal 98-year-old man. Calculated digoxin recovery was 243 μg, or 2 days' worth of his previous parenteral maintenance dose, or 36.3% of a therapeutic loading dose.

Discussion. In these three patients with renal failure XAD-4 HP removed digoxin at a rate exceeding normal renal digoxin clearance, greatly reduced plasma T½ digoxin, cleared digoxin from RBCs, and ameliorated symptoms and signs of digitoxicity.

Digoxin in the blood compartment is distributed in plasma, where 25% is protein-bound in normal subjects (perhaps less in uremics), and in RBCs, where it is largely bound to surface Na+ K+ ATPase [1, 3]. In our studies the extraction of digoxin from the plasma by the resin was extremely efficient, and the negligible or low outflow digoxin concentrations during most of the procedures indicate that protein-bound as well as free digoxin was probably removed. Digoxin was also extracted from RBC membranes with an efficiency only slightly less than that of plasma digoxin extraction. There was only a modest decline in extraction fraction during each procedure. Plasma and whole blood digoxin clearances greatly exceeded renal digoxin clearance in comparable patients with normal renal function. Plasma and RBC digoxin were removed at a rate greater than the ability of tissue stores to equilibrate with the blood compartment. Thus, quantitative digoxin extraction progressively decreased throughout each procedure despite maintenance of high clearances, and plasma digoxin rebounded to

Table 2. XAD-4 hemoperfusion in patient 2: 63 years old, 72 kg, Ht 26%, K^+ 5.5 mEq/liter, C_{Cr} 2 ml/min[a]

Time *hours*	Q_B	Q_P	Plasma digoxin A	V	EF	Cl	T½	RBC-surface digoxin A	V	EF	Cl	Total digoxin clearance *(plasma + RBC) ml/min*
HP												
Start												
0	175	130	6.2									
0.05	200	152	5.4	0.3	0.94	139		5.0	0.9	0.82	31	170
1.25	200	152	4.4	0.6	0.86	127						
2.25	250	185	4.6	1.0	0.78	144	6					
3.25	250	185	4.4	1.2	0.73	135		4.0	1.2	0.70	46	181
4.25	250	185	3.8	1.2	0.68	124						
5.25	250	185	3.6	1.0	0.72	133		4.0	1.1	0.73	47	170
End												
6.75			4.2									
8.75			5.0									
10.75			5.2									
19.25			5.0				76					
41.25			4.9									
53.25			3.5									
77.25			3.3									

[a] For abbreviations, see Table 1.

Table 3. XAD-4 hemoperfusion patient 3: 98 years old, 67 kg, Ht 28%, K^+ 4.7 mEq/liter, C_{Cr} 4.6 ml/min[a]

Time *hours*	Q_B	Q_P	Plasma digoxin A	V	EF	Cl	T½	RBC-surface digoxin A	V	EF	Cl	Total digoxin clearance *(plasma + RBC) ml/min*
Pre HP												
−12.5			4.0									
HP							54.5					
Start												
0	100	72	3.4					4.3				
0.25	350	252	3.1	<0.5	0.92	229		4.0	0.8	0.80	81	310
1.25	350	252	2.5	<0.5	0.90	224		3.0	1.1	0.63	64	288
2.25	350	252	2.2	<0.5	0.89	222		2.6	1.3	0.50	59	281
3.25	350	252	2.1	<0.5	0.89	219	4.8	2.4	2.0	0.20	20	239
4.25	350	249	1.8	<0.5	0.86	214		2.5	0.5	0.80	81	295
5.25	350	249	1.6	<0.5	0.84	210		2.5	0.8	0.68	69	279
6.25	350	249	1.6	<0.5	0.84	210		2.1	0.7	0.67	68	278
6.75	350	249	1.6	<0.5	0.84	210		2.2	0.9	0.59	60	270
End												
14.25			2.5									

[a] For abbreviations, see Table 1.

levels intermediate between pre- and postprocedure levels, several hours after HP was discontinued.

The usefulness of this treatment for digoxin toxicity is disputed, even in patients with renal failure. It has been stated that for drugs with large volumes of distribution, such as digoxin, clearance of the plasma compartment, however efficient, could not remove enough drug to ameliorate toxicity [4]. We counter with the following arguments: First, the toxic/therapeutic ratio of digoxin is very low, and the removal of the modest amounts of drug would, in most cases, be sufficient to reverse toxicity. Second, the volume of distribution of digoxin is reduced in subjects with renal failure, so they require less digoxin to achieve therapeutic and toxic levels and less digoxin removal to reverse toxicity. In addition a greater proportion of the drug is present in the blood compartment and readily available for extraction [5, 6]. Third, the calculated or quantified amount of digoxin removed from these patients was considerable, representing a significant proportion of an ideal loading dose of digoxin for patients with renal failure which was 10 μg/kg [6], and 2 to 4 days' worth of their previous maintenance doses. Fourth, digoxin clearance by HP greatly exceeded normal renal digoxin clearances. The maintenance of optimal renal digoxin clearance is the cornerstone of management of any digitoxic patient, and the reason for digoxin toxicity in most patients with renal insufficiency is their lack of normal renal digoxin excretion. The resolution of digoxin toxicity should be hastened by supplying to such subjects, albeit temporarily, digoxin clearances greater than normal renal digoxin clearance. Fifth, improvement in digitoxic symptoms and signs was observed in all patients studied, with each treatment.

Our experience indicates that treatment is most efficient at high blood flow rates, because, while extraction fraction might

decline as flow increases, this is probably outweighed by the increased clearances achieved. Owing to slow equilibration of tissue stores with the blood compartment, quantitative digoxin extraction would also be maximized by several short treatments (if needed) separated by a few hours to allow equilibration and rebound of blood levels, rather than a single protracted treatment.

We feel that XAD-4 hemoperfusion properly performed can abbreviate the course of digoxin toxicity in patients with renal failure and deserves wider application and investigation.

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